UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF CALIFORNIA

IN RE: INCRETIN-BASED THERAPIES PRODUCTS LIABILITY LITIGATION *This Document Relates to All Cases*	Case No. 13-md-2452-AJB-MDD **Hon. Anthony J. Battaglia**

PLAINTIFFS' BRIEF ON THE SEQUENCING OF DISCOVERY AND CAUSATION

> [D]efendants always deny liability when faced with a meritorious lawsuit. Merck didn't roll over and play dead when it was first sued over the people it killed while raking in billions selling Vioxx. Merck was brought to heel only when counsel obtained—through discovery—internal documents making it clear that Merck continued hawking a drug that it knew induced heart attacks in unsuspecting patients.

—Judge Alex Kozinski, *Opposition to Final Approval of Class Action Settlement*, 12-cv-08238-BRO-PJW, ECF 71 (C.D. Cal. Nov. 10, 2013) (attached as Exhibit "E").

SUMMARY OF ISSUE

More than a year ago, after this Court ordered the parties to agree upon a case management schedule[1], the parties negotiated and submitted[2] the same tried-and-true discovery and dispositive motion scheduling required by the Federal Rules of Civil Procedure and implemented in all comparable pharmaceutical MDLs, including the Actos,[3] Avandia,[4] Baycol,[5]

[1] *See, e.g., Scott v. Merck et al.*, 12-cv-02549-AJB-MDD, ECF 20 (S.D. Cal. Dec. 28, 2012) and *Haqq v. Amylin et al.*, 12-cv-02572-AJB-MDD, ECF 12 (S.D. Cal. Dec. 28, 2012). Note: Novo Nordisk was not a party to these agreements due to its later addition as a Defendant in these proceedings.

[2] The Parties Joint Rule 26(f) Conference Report and Discovery Plan was submitted to the Court by email on January 31, 2013. *See* Exhibit "H".

[3] *In re Actos (Pioglitazone) Prods. Liab. Litig.*, 11-md-02299-RFD-PJH, ECF 1418 (W.D. La. July 13, 2012).

Chantix,[6] Levaquin,[7] Pradaxa,[8] Vioxx,[9] and Yaz[10] MDLs.[11] Now, however, Defendants propose an unprecedented schedule in which Plaintiffs' general causation expert reports are due in less than 90 days — months before discovery into any issue (including general causation) could be completed[12], and thus well before Plaintiffs could even select the best experts to suit the available evidence, much less obtain and provide those experts with the wealth of research and clinical data that Defendants are obligated to retain. Accordingly, this Court must decide whether to use the standard schedule — as agreed to previously by the parties and thereafter endorsed by the

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[4] *In re Avandia Marketing, Sales Practices and Prods. Liab. Litig.*, 07-md-01871-CMR, ECF 564 (E.D. Pa. Dec. 3, 2009).

[5] *In re Baycol Products Litigation*, 01-md-01431-MJD-SER, ECF 3679 (D. Minn. Oct. 17, 2003).

[6] *In re Chantix (Varenicline) Prods. Liab. Litig.*, 09-cv-02039-IPJ, ECF 25 (N.D. Ala. Feb. 24, 2010).

[7] *In re Levaquin Prods. Liab. Litig.*, 08-md-01943-JRT, ECF 132 (D. Minn. Feb. 20, 2009).

[8] *In re Pradaxa (Dabigatran Etexilate) Prods. Liab. Litig.*, 12-md-02385-DRH-SCW, ECF 154 (S.D. Ill. April 9, 2013).

[9] *In re Vioxx Prods. Liab. Litig.*, 05-md-01657-EEF-DEK, ECF 1023 (E.D. La. Oct. 11, 2005).

[10] *In re Yasmin and Yaz (Drospirenone) Marketing, Sales Practices and Prods. Liab. Litig.*, 09-md-02100-DRH-PMF, ECF 1735 (S.D. Ill. May 18, 2011).

[11] In the Viagra litigation, the parties agreed to an accelerated "general causation" discovery schedule in which general causation fact discovery was completed first, followed by general causation expert discovery and summary judgment motions. *In re Viagra Prods. Liab. Litig.*, 06-md-01724-PAM, ECF 38 (D. Minn. June 30, 2006). Defendants do ***not*** propose the Viagra schedule, they propose a schedule in which virtually no fact discovery is taken on general causation prior to expert discovery.

[12] Pharmaceutical MDLs are not models of efficiency, and often result in sanctions against the Defendants for discovery abuse and for destruction of evidence. *See, e.g.*, *In re Pradaxa (Dabigatran Etexilate) Prods. Liab. Litig.*, 12-md-02385, ECF 320, 334 (S.D. Ill.); *see also In re Actos (Pioglitazone) Prods. Liab. Litig.*, 11-md-02299-RFD-PJH, ECF 3933 (W.D. La., Jan. 30, 2014) (finding intentional destruction of documents and violations of Fed. R. Civ. P. 37, and deferring sanction until after trial).

Court in its February 13, 2013 case management order[13] — or to needlessly generate a year of collateral litigation for the sole purpose of denying Plaintiffs' experts' access to Defendants' data.

As the Plaintiffs explained at Science Day, all Plaintiffs request is that causation be evaluated on "the sum of all the evidence." Defendants, in turn, request that causation be evaluated on 'all' the evidence…except the evidence in their possession.

ARGUMENT

I. PLAINTIFFS' PROPOSAL IS CONSISTENT WITH THE FEDERAL RULES AND WITH THE PRACTICAL REALITY OF THIS LITIGATION

Drug manufacturers have vastly more information about a drug's safety than all other sources combined, including the government. They bear the burden of initially proving their drug's efficacy and safety through clinical trials, and then of ensuring their drug's safety by collecting and reviewing clinical data from health professionals across the country: "it has remained a central premise of federal drug regulation that the manufacturer bears responsibility for the content of its label at all times. It is charged both with crafting an adequate label and with ensuring that its warnings remain adequate as long as the drug is on the market." *Wyeth v. Levine*, 555 U.S. 555, 570–571 (2009).[14] Thus, by design, most of the evidence regarding the

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[13] Attached hereto as Exhibit "A".

[14] See also *id.* (*citing* 21 CFR § 201.80(e) (requiring a manufacturer to revise its label "to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug"); § 314.80(b) (placing responsibility for postmarketing surveillance on the manufacturer); 73 Fed. Reg. 49605 ("Manufacturers continue to have a responsibility under Federal law . . . to maintain their labeling and update the labeling with new safety information.")). *See also* 21 U.S.C. § 355(k)(1) and 21 CFR § 314.80 and § 314.81 (requiring an applicant to establish and maintain records and to report data relating to clinical experience, along with other data or information, for drugs for which an approved application is in effect).

safety of a drug product that might impact general causation is within the drug manufacturer's own records.[15]

The Federal Rules of Civil Procedure account for this very possibility, *i.e.*, that the bulk of evidence material to an element of a plaintiff's claim would be within the defendant's control, and the Rules recognize that it would be unjust to allow a defendant to move for summary judgment while the defendant has not produced critical evidence. Federal Rule 56(d)[16] provides a mechanism for exactly this circumstance, through which the nonmoving party can obtain further discovery before summary judgment is decided.[17]

Plaintiffs' proposal establishes the same workable discovery→ experts→ motions→ trial case management schedule that is currently guiding multiple pharmaceutical MDLs and the vast majority of complex

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[15] If, going forward, the Defendants would like to establish a system in which all of their data are automatically forwarded to plaintiffs' lawyers, the PSC is happy to oblige them.

[16] Fed. R. Civ. P. 56(d) ("When Facts Are Unavailable to the Nonmovant. If a nonmovant shows by affidavit or declaration that, for specified reasons, it cannot present facts essential to justify its opposition, the court may: (1) defer considering the motion or deny it; (2) allow time to obtain affidavits or declarations or to take discovery; or (3) issue any other appropriate order.")

[17] *See, e.g.*, *Jasco Tools, Inc. v. Dana Corp. (In re Dana Corp.)*, 574 F.3d 129, 149 (2d Cir. 2009) ("[A] party against which summary judgment is sought must be afforded 'a reasonable opportunity to elicit information within the control of his adversaries.'") (quoting *Quinn v. Syracuse Model Neighborhood Corp.*, 613 F.2d 438, 445 (2d Cir. 1980) (summary judgment should not be granted against nondilatory party who has been 'denied reasonable access to potentially favorable information')). *Accord Employers Teamsters Local Nos. 175 & 505 Pension Trust Fund v. Clorox Co.*, 353 F.3d 1125, 1129 (9th Cir. 2004) (further discovery required where nonmoving parties makes "(a) a timely application which (b) specifically identifies (c) relevant information, (d) where there is some basis for believing that the information sought actually exists.").

federal civil cases. The sole difference is that, given the multiple defendants and products at issue here, Plaintiffs have staggered the schedules so that the litigation is not overwhelmed with simultaneous summary judgment motion practice and bellwether trials.[18] This arrangement is sensible and workable, and Defendants have not raised any genuine objection to it, but have instead firmly demanded that Plaintiffs be precluded from completing general causation discovery before expert discovery and *Daubert* challenges commence.

Plaintiffs' research disclosed only one example in which a "general causation first" approach was taken in a pharmaceutical MDL[19]: Viagra, in which the parties agreed to *conduct general causation fact discovery* and then move into expert discovery and motions on general causation. The merits of such a proposal are debatable — given the breadth of ESI and the number of depositions needed here, segregating general causation discovery from other discovery would likely prove unworkable — but such is not what Defendants here have suggested.[20]

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[18] The three orders proposed by Plaintiff are attached hereto as Exhibit "B" (Lilly and Amylin), Exhibit "C" (Novo), and Exhibit "D" (Merck). The staggered schedules are designed to deal with certain realities – e.g., the Lilly and Amylin cases should be tried first due to the amount of discovery already gathered as a result of their involvement in the JCCP. Additionally, by way of further example, market share dictates putting the Novo cases, which represents only 27 of 262 total cases in the MDL, at the back-end of staged discovery. Finally, staged discovery itself is highly logical as the Court can only try one case at a time and it would be a waste of the Court's and the Parties' resources to work up more cases than can be tried at any given time.

[19] Outside of the pharmaceutical context, the Court in *In re Human Tissue Products Liability Litigation*, MDL No. 1763 permitted an early motion on general causation. There, the defendants had no more information than the plaintiffs on whether dead tissue could carry disease after a certain amount of time, and so the question could be addressed early on the basis of publicly-available information, with no prejudice to the plaintiffs.

[20] The Viagra MDL is itself a cautionary tale: less than a year after the District Court granted summary judgment on general causation for the defendant, the FDA cited Pfizer for "misclassifying and/or downgrading

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II. DEFENDANTS' PROPOSAL WOULD MULTIPLY THE WORK TO BE DONE BY THE COURT AND THE PARTIES WITHOUT PROVIDING ANY REAL BENEFIT

For good reason, no court has ever entertained the Defendants' proposal; the notion that general causation in a drug case should be decided without reference to the drug manufacturer's own data is ludicrous. Such would be *worse* than deciding a malpractice case without the medical records, or a Fourth Amendment case without the arrest records, because in both of those situations the records are merely the impressions of the defendants — drug companies, however, are obliged to retain reams of *raw* data that can be reviewed later, like clinical trial data and adverse event reports. This situation is more akin to determining a data breach case without first seeing the encryption used by the defendant.[21]

An attempt to decide *Daubert* challenges in advance of general causation discovery is not putting the cart before the horse, it is forgoing the horse entirely. *Daubert* is "a preliminary assessment of whether the reasoning or methodology underlying the testimony is scientifically valid and of whether that reasoning or methodology properly can be applied to the facts in issue." *Daubert*, 509 U.S. at 592-93. Here, based on the available public data, Plaintiffs have a *prima facie* case for general causation[22], but

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reports [of the same condition alleged in the MDL] to non-serious without reasonable justification." FDA WARNING LETTER NYK 2010-19, *available at* <http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm215405.htm>

[21] *See In re Sony Gaming Networks & Customer Data Sec. Breach Litig.*, 11-md-2258-AJB-MDD, 2014 U.S. Dist. LEXIS 7353, at *115 (S.D. Cal. Jan. 21, 2014) (denying motion to dismiss and noting need to assess defendants' encryption).

[22] A prima facie general causation case based upon published studies is

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Plaintiffs do not have anywhere near the full data available — data which the Defendants are obligated by the FDA to retain for the precise purpose of assessing drug safety — because the Defendants have not produced it. That data would, in turn, both inform Plaintiffs' experts' "reasoning or methodology" and comprise many of "the facts in issue." Such is why the Manual For Complex Litigation (4th Edition) repeatedly advises courts to allow adequate discovery before attempting to decide scientific issues.[23]

In addition to the problems specific to *Daubert* that would be caused by Defendants' proposal, the proposal suffers two fatal procedural defects. First, although drug companies have variously referred to this proposal as "science first" or "*Daubert* first," the Federal Rules of Civil Procedure do not provide such a procedural shortcut. *Daubert* itself interprets a Rule of Evidence.[24] The sole basis on which this Court could review the sufficiency

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enough to survive a *Daubert* challenge, though presumably Defendants disagree. *See, e.g., In re Actos (Pioglitazone) Prods. Liab. Litig.*, 11-md-02299-RFD-PJH, ECF 3823 (W.D. La., Jan. 6, 2014) (rejecting *Daubert* challenge to general causation expert opining that Actos can cause bladder cancer), discussed *infra*.

[23] *See, e.g.*, Manual for Complex Litigation (4th ed.) § 11.481 at 98 ("Scheduling should take into account that the parties may lack sufficient information to select expert witnesses until the issues have been further defined and certain discovery is completed…") § 22.87 at 441 ("Generally, the more novel, complex, and central the scientific or technical issues, the more time the parties will need to conduct discovery, prepare expert reports, and brief the issues for a Daubert hearing.") § 23.32 at 497 ("In toxic tort cases, submission of expert reports may not be appropriate until factual discovery has been completed.") § 23.33 at 499 ("Parties need adequate time for experts to be retained and to prepare their reports before the required disclosures are due.").

[24] For purposes of the record, Plaintiffs preserve their objection to this Court hearing *Daubert* challenges. *Lexecon, Inc. v. Milberg Weiss Bershad Hynes & Lerach*, 523 U.S. 26, 34-35 (1998) requires remand of actions prior to trial, and evidentiary matters — like *Daubert* — are plainly trial rulings. MDL courts often remand cases in advance of *Daubert*. *See, e.g., In re Aredia & Zometa Prods. Liab. Litig.*, 06-md-01760 (M.D. Tenn. Dec. 22, 2010). Plaintiffs would prefer to work out a *Lexecon* waiver at a later date, but

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of Plaintiffs' general causation evidence is by way of a motion for partial summary judgment on general causation. Defendants' proposal would thus create a procedural quagmire in which the Plaintiffs and the Court are stuck addressing repeated Rule 56(d) responses to delay consideration of the Defendants' motions, because discovery would still be ongoing. *Daubert* thus could not be decided until the close of discovery anyway.

Second, if the Court denies any of these FRCP 56(d) motions and moves towards expert discovery and *Daubert* while discovery is ongoing, then the parties and the Court would be thrown into the Sisyphean task of repeatedly addressing "supplemental" Plaintiffs' expert reports that have been amended to address new information obtained in discovery.[25] Under Defendants' proposal, expert discovery and the *Daubert* hearing would take place from April through November of this year, with generic discovery ending in December — and throughout that entire process Plaintiffs would be forced to repeatedly update their expert reports and briefs in light of new evidence (and to repeatedly request follow-up depositions of Defendants' experts), and the Court will be obliged to decide all of these collateral issues that arise, and to sporadically reconsider orders and throw away briefing in light of updated information.

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under the present circumstances it seems the Defendants will not even agree to use standard case management procedures.

[25] Under Fed. R. Civ. P. 37(c)(1), "If a party fails to provide information or identify a witness as required by Rule 26(a) or (e), the party is not allowed to use that information or witness to supply evidence on a motion, at a hearing, or at a trial, *unless the failure was substantially justified or is harmless*." *See Torres v. City of Los Angeles*, 548 F.3d 1197 (9th Cir. 2008) (applying to expert disclosures). Late production of a supplemental expert opinion due to *Defendants* not producing the relevant evidence upon which the opinion is based would be both "substantially justified" and "harmless."

Yet, there is no prize at the end of Defendants' labyrinth: the Defendants' proposed *Daubert* hearing is merely one month before their proposed close of discovery. The acceleration of general causation expert discovery will thus not save the Court and the parties from the same work that would have occurred anyway, it will simply generate additional work while the Court attempts to simultaneously perform two tasks (discovery and *Daubert*) that logically must be done sequentially.

III. DEFENDANTS' SELF-SERVING CONCLUSIONS ABOUT THEIR OWN DATA ARE NOT RELIABLE, MUCH LESS ENTITLED TO COMPLETE DEFERENCE BY THE COURT

As Judge Kozinski wrote, "The simple fact is, no one knows better the problems with a vehicle or any other product than the company that makes it. It's their job to know, and it's the job of the lawyers suing them to find out everything the company knows and hopes to conceal."[26] Defendants will presumably respond to the above concerns with the same *ipse dixit* assertions that have earned the pharmaceutical industry reprimands across the country,[27] claiming that their public conclusions about their wealth of

[26] Kozinski, *supra*, Opposition (attached as Exhibit "E").

[27] *See, e.g.*, *Lance v. Wyeth*, No. 18 EAP 2011, 2014 Pa. LEXIS 205, at *46 (Jan. 21, 2014) ("in its brief, Wyeth generally cast its own conduct, and that of pharmaceutical companies at large, in the best possible light. This, of course, leaves the impression that Appellee's assertion of a lack of due care is a marginal aspect of the case. Indeed, this liberty pervades Wyeth's arguments ..."); *Allen v. Takeda Pharms. N. Am. (In re Actos (Pioglitazone) Prods. Liab. Litig.)*, 11-md-2299, 2014 U.S. Dist. LEXIS 5289, at *47–48 (W.D. La. Jan. 14, 2014) ("Defendants are, again, cautioned as to their propensity to provide and argue only selected portions of challenged information and to exclude those portions of the information which, on its face, undercuts Defendants' arguments. Such practice does not serve counsel or their clients well. Defendants have repeatedly argued, in Daubert motions, that a statistically significant finding is much more important and reliable than a finding with no statistical significance. Consequently, when given a fair and full reading, the Defendants' argument is at its *very best,* perplexing.")

data should simply be trusted as infallible, and that there is no need for Plaintiffs or their experts to review the actual analyses, communications, adverse event reports, and clinical data.

At a minimum, drug companies are prone to "wishful thinking, not a critical interpretation of the data," and to making "interpret[ations] to support a preconceived hypothesis," as *an associate director at Merck Research Laboratories* described Merck's internal Vioxx research, three years before the drug was withdrawn from the market, and two years after the dangers were plainly apparent.[28] More accurately, Merck "made inaccurate, unsupported, or misleading statements about Vioxx's cardiovascular safety in order to increase sales of the drug," as the Department of Justice described it when Merck plead guilty to misbranding Vioxx and settled the government's civil claims.[29] Other defendants in this litigation, too, have paid significant sums to resolve accusations by the federal government that they fraudulently marketed their products.[30] Again, per Judge Kozinski, "There are countless other cases where companies have played possum until they were confronted with internal documents proving them liable" — and that is, apparently, exactly what the Defendants hope to avoid with

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[28] See *Vioxx and the Merck Team Effort*, Kenan Institute for Ethics, p.8 <https://kenan.ethics.duke.edu/wp-content/uploads/2012/07/Case-Study-Vioxx.pdf>, *quoting* MRK-ACF0005697, *available at* <http://dida.library.ucsf.edu/pdf/oxx03v10>.

[29] "U.S. Pharmaceutical Company Merck Sharp & Dohme Sentenced in Connection with Unlawful Promotion of Vioxx," Department of Justice press release, April 19, 2012, *available at* <http://www.justice.gov/opa/pr/2012/April/12-civ-497.html>.

[30] *See, e.g.*, "Eli Lilly and Company Agrees to Pay $1.415 Billion to Resolve Allegations of Off-label Promotion of Zyprexa," Jan. 15, 2009, *available at* <http://www.justice.gov/opa/pr/2009/January/09-civ-038.html>, "Danish Pharmaceutical Novo Nordisk to Pay $25 Million to Resolve Allegations of Off-Label Promotion of Novoseven," June 10, 2011, *available at* <http://www.justice.gov/opa/pr/2011/June/11-civ-764.html>.

their unprecedented scheduling. Even the scant document productions to date reveal the actual concerns of Defendant Lilly; in one email, their own researcher admits that their real concern is not whether their product causes a cancer with a 14% five-year survival rate even if caught immediately, but whether regulatory officials and the public might get wind of the risks of Incretin-based therapies, ruining sales of the whole family of drugs.[31] With a multi-billion dollar class of products on the line, the possibility Defendants would be motivated to delay and or deny full discovery is real and palpable. Indeed, it appears to be playing out in this very dispute.

IV. DEFENDANTS HAVE PRODUCED VIRTUALLY NONE OF THE INFORMATION UPON WHICH AN EXPERT ASSESSING GENERAL CAUSATION WOULD RELY

Thus far, Defendants as a whole have produced little of substance relating to general causation. Plaintiffs previously served on all Defendants discovery (both requests for documents and deposition notices) on a wide variety of topics, including, adverse event reports. In response, Merck and Novo produced only objections. Eli Lilly and Amylin produced objections and generalized references to its production in the JCCP, despite this Court's order saying such would be insufficient.[32]

For example, here is part of an objection to a request asking for Eli Lilly's policies applicable to the identification and investigation of adverse events:

> Lilly further objects to this request on the ground that the terms "all documents and ESI" and "all written policies" are overly broad and unduly burdensome. Lilly has had numerous policies and procedures over the period at issue that relate, to varying degrees, to the collection, processing and reporting of adverse event reports for Byetta®, many of which have at best only marginal relevance to the disputed issues in this litigation and for which the burden of identification, collection and production would outweigh any benefit. Lilly objects

[31] *See* Lilly 00887702, which is confidential, but will be produced for in camera inspection, if requested.

[32] *See* ECF 257.

Lilly Objections To Plaintiffs' Second Set of Requests, p. 14, attached as Exhibit "F". Plainly, these policies are not of "marginal relevance," they are central to both breach of duty and general causation. When Plaintiffs and their experts review Lilly's adverse event reports, they will need to know the criteria Lilly used in "collecting, processing and reporting" that information, or they will not be able to assess the quality of the information contained in those reports, nor will they know where to look in Lilly's files for events that were not properly coded or investigated.[33]

Amylin, in turn, has generally refused to respond to requests for a rather curious reason:

> Steering Committee. Amylin is willing to meet and confer with Plaintiffs' counsel in order to create an orderly process for propounding centralized discovery in this litigation. But until the parties agree on such an orderly, centralized process or one is created by order of the Court, Amylin will not respond substantively to any further written discovery requests.

See *Amylin Objections To Plaintiffs' Second Set of Requests*, attached as Exhibit "G".

There is such a "centralized" process in place: it is the MDL. As this Court ordered, "The existence of ESI has not changed the basics of discovery. It is upon Plaintiffs to make specific discovery requests under the Rules. It is then upon Defendants to conduct reasonable searches for responsive, non-privileged information within their possession, custody or control and produce such information or make particularized objections when warranted."[34] Amylin apparently disagrees.

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[33] Eli Lilly has previously been warned by the FDA for misrepresenting adverse event data. *See* Warning Letter of September 25, 2008, *available at* <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCompanies/ucm054007.pdf>.

[34] *See* ECF 257.

Plaintiffs are still optimistic that the Parties will resolve these issues without court intervention, and their disposition is not ripe here as the Parties are working together in this regard, but the point is simple: the Defendants have extensive data material to the general causation analysis they have not yet produced, and the Court has not yet even been presented these issues for resolution. A genuine, thorough review by Plaintiffs and their experts cannot occur under those circumstances, nor can a genuine *Daubert* analysis.

V. DEFENDANTS HAVE NOT SHOWN THAT THIS LITIGATION WOULD BE STREAMLINED BY FRONTLOADING GENERAL CAUSATION ISSUES

As noted above, Defendants do *not* propose a "general causation first" schedule, as was used by agreement in the Viagra MDL, in which the litigation focuses on general causation before expanding to other issues. Rather, Defendants vehemently oppose any general causation discovery at all, and instead propose Plaintiffs' experts be hamstrung and left to use only publicly available data and studies, without the benefit of the Defendants' own materials, which are *by law* the most extensive repository of clinical and experimental data on their drugs. Nonetheless, for purposes of completeness, Plaintiffs here address a hypothetical "general causation first" schedule.

As Judge Alsup concluded while rejecting a similar proposal:

> Defendants have not demonstrated sufficient justification for their request. The Court construes the instant motion as a variation on defendants' previous request for phased discovery. The Court has not changed its view that setting an earlier deadline, even on one issue, will likely result in increased costs for all involved. Defendants may be right that following a *Daubert* hearing and summary

> judgment motions on the issue of general causation much of plaintiffs' case might fall away. But that is only speculation. In the Court's view the better approach is to wait until discovery closes. Expedited discovery on one issue, along with the time and expense put into preparing for other hearings—which may or may not be successful—could realistically result in delays on other discovery if defendants are unsuccessful.

Gonzales v. Texaco, No. 06-02520, 2007 WL 661914 (N.D. Cal. Feb. 28, 2007). A "general causation first" schedule can, in theory, reduce costs *if* (a) the Defendants do not abuse the limitation in discovery by obstructing discovery that could be material to general causation *and* (b) there is a strong likelihood of the litigation as a whole being dismissed pretrial.

The former is plainly not the case here; the Defendants have been highly resistant to discovery, refusing and or delaying the production of even basic discovery that is ordered to be produced in all drug litigation, like the adverse event data and the full data (including studies and raw numbers) underlying the New Drug Application.

The latter is also not the case; for all the Defendants' feigned confidence that this litigation will be wholly disposed over on *Daubert* grounds, Plaintiffs are capable of presenting scientific evidence supporting general causation, and thus Defendants' claims that this litigation can be resolved on general causation are at a minimum "speculation," as in *Gonzales*, and are more likely demonstrably wrong. Yet, the point here is not whether Plaintiffs can establish general causation at this juncture, but whether it is *possible* that, after ***full*** discovery — including the Defendants' production of documents upon which their own claims of safety rely — the Plaintiffs will be able to establish general causation. As shown below, Plaintiffs' contentions about general causation are already well-supported by available public evidence, but neither the parties' experts nor the Court

will be in the position to truly assess general causation until the Defendants have produced the evidence (*all* of it) in their possession.

As this Court has recognized, "it is well settled that there are few if any certainties in science, *Daubert*, 509 U.S. at 590, and *Daubert* was not intended to impose an 'exacting standard of causality' beyond the preponderance of the evidence 'simply because scientific issues are involved.'" *Johns v. Bayer Corp.*, No. 09-cv-1935 AJB-DHB, 2013 U.S. Dist. LEXIS 51823, at *49–50 (S.D. Cal. Apr. 10, 2013).[35] As the advisory committee note to Fed. R. Evid. 702 says, "the rejection of expert testimony is the exception rather than the rule," and, "As the Court in *Daubert* stated: 'Vigorous cross-examination, presentation of contrary evidence, and careful instruction on the burden of proof are the traditional and appropriate means of attacking shaky but admissible evidence.'" Further, "The first several victims of a new toxic tort should not be barred from having their day in court simply because the medical literature, which will eventually show the connection between the victims' condition and the toxic substance, has not yet been completed." *Turner v. Iowa Fire Equip. Co.*, 229 F.3d 1202, 1209 (8th Cir. 2000). Such is why a medical expert does not always have to cite to published studies on general causation in order to establish causation and, under the right circumstances, even a differential diagnosis may reliably form the basis of an opinion that a particular item caused an injury. *Hollander v. Sandoz Pharm. Corp.*, 289 F.3d 1193, 1211-12 (10th Cir. 2002). As described below, multiple studies are *already* underway to further understand the link between Incretin-based therapies and

[35] Citing *In re Ephedra Prods. Liab. Litig.*, 393 F. Supp. 2d 181, 190 (S.D.N.Y. 2005); *In re Heparin Prods. Liab. Litig.*, 803 F. Supp. 2d 712, 743 (N.D. Ohio 2011) (stating that the court "will not exclude expert testimony on the basis that the evidence supporting it does not establish causation to a scientific certainty").

pancreatic cancer, and it appears the Defendants' rush to *Daubert* is calculated to avoid giving Plaintiffs' experts the benefit of Defendants' own files and those studies in the works.

Courts in other pharmaceutical MDLs have rejected the myriad *Daubert* challenges raised by drug companies that are plainly better suited for cross-examination, like claims that an expert in one field is unqualified to even consider information from other fields[36], or that experts are "cherry-picking" if they prefer one study over another.[37] The recent *Daubert* decisions in the Actos litigation are instructive; defendant there made all the same assertions as Defendants here, claiming that the *only* admissible proof that a drug could cause cancer would be a unanimous series of randomized controlled trials with data pruned in exactly the way the defendant proposed.[38] The Actos court flatly rejected these arguments through a series of opinions.[39]

The Actos court's ruling on "Development of Bladder Cancer Within One Year of Exposure" is particularly instructive here, as it involved many similar issues.[40] For example, the Court thoroughly dispensed with the

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[36] "[I]t is common in technical fields for an expert to base an opinion in part on what a different expert believes on the basis of expert knowledge not possessed by the first expert . . . ." *In re Nuvaring Prods. Liab. Litig.*, 2013 U.S. Dist. LEXIS 31025, at *64 (E.D. Mo. Mar. 4, 2013) (quoting *Dura Auto. Sys. of Ind., Inc. v. CTS Corp.*, 285 F.3d 609, 613 (7th Cir. 2002)).

[37] "Allegations that Plaintiffs' experts 'cherry picked,' or cited only to data that supported their opinion and ignored unfavorable data, must wait until cross-examination." *In re Nuvaring Prods. Liab. Litig.*, U.S. Dist. LEXIS 31027, at *68 (E.D. Mo. Mar. 5, 2013) (citing *Kuhn v. Wyeth, Inc.*, 686 F.3d 618, 633 (8th Cir. 2012)).

[38] Not coincidentally, Defendants' proposed pruning of the data resulted in as low a cancer risk as possible.

[39] The opinions are available at <http://www.lawd.uscourts.gov/rulings-court>.

[40] *In re Actos (Pioglitazone) Prods. Liab. Litig.*, 11-md-02299-RFD-PJH, ECF 3771 (W.D. La. July 13, 2012)., *available at*

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defendant's claim that general causation could only be shown through a single study proving causation:

> *No Single Study Answers All Questions.* During oral argument, counsel for the defense asserted that the Plaintiffs' theory of causation is unreliable because it has "never been shown to occur." Upon this Court's request for clarification, it became evident the Defendants suggest the Plaintiffs' *theory* is not reliable - and should not be allowed to be relied upon by the jury – because there is no *one study* that has demonstrated the causal link between Actos® and bladder cancer. This argument was not made explicitly in the Defendants' briefs, and at oral argument, argument to explain, or demonstrate, how or why a scientific theory must be demonstrated with *one single study* was not given. However, nowhere has this Court heard or seen, on the part of the Defendants, argument or evidence to explain why a given theory must be deemed wholly unreliable merely because it requires multiple steps to prove, particularly if each of those steps cannot be shown to be unreliable in and of themselves, and if a proper scientific methodology was employed, by otherwise qualified experts in their respective fields. Neither has this Court found jurisprudence from its independent review suggesting such a limitation of expert opinion testimony that is otherwise grounded in sound scientific methodology and evidence. Defendants' argument on this point, also, is not persuasive.

As shown at Science Day, Plaintiffs *already* have studies which, when viewed together, establish the capacity of Incretin-based therapies to cause pancreatic cancer. On the most basic level, it is well-established that Incretin-based therapies can cause inflammation in the pancreas, and that

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<http://www.lawd.uscourts.gov/sites/default/files/UPLOADS/11-md-2299.121913.Allen.Daubert.One.Year.Doc3771.pdf>.

repeated inflammation can lead to chronic pancreatitis, and there is a strong link between chronic pancreatitis and pancreatic cancer.[41] On a cellular level, GLP-1 is known to stimulate cell proliferation,[42] and exogenous GLP-1R agonists and DPP-4 inhibitors can increase cell proliferation and decrease cell apoptosis.[43] Such a finding *alone* would suggest a capacity to cause cancer, but a closer link has been drawn: "GLP-1 mimetic therapy may induce focal proliferation in the exocrine pancreas and, in the context of exocrine dysplasia, may accelerate formation of neoplastic PanIN lesions …"[44]

As would be expected, these exact changes have been found in actual humans, with examinations of pancreata revealing that "incretin therapy in humans resulted in a marked expansion of the exocrine and endocrine pancreatic compartments, the former being accompanied by increased proliferation and dysplasia and the latter by α-cell hyperplasia with the potential for evolution into neuroendocrine tumors."[45] Again as expected, epidemiological studies have shown a substantial increase in pancreatic

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[41] *See, e.g.*, Raimondi, et al., "Pancreatic cancer in chronic pancreatitis; aetiology, incidence, and early detection," Best Practice & Research Clinical Gastroenterology, Vol. 24, Issue 3, June 2010, pgs. 349–58.

[42] *See, e.g.*, List, et al., "Glucagon-like peptide 1 agonists and the development and growth of pancreatic beta-cells." Am. J. Physiol. Endocrinol. Metab. 2004 Jun:286(6):E875-81.

[43] *See, e.g.*, Portha, et al., "Activation of the GLP-1 receptor signalling pathway: a relevant strategy to repair a deficient beta-cell mass," Exp Diabetes Res. 2011;2011:376509. doi: 10.1155/2011/376509. Epub 2011 May 22.

[44] Gier, et al., "Chronic GLP-1 receptor activation by exendin-4 induces expansion of pancreatic duct glands in rats and accelerates formation of dysplastic lesions and chronic pancreatitis in the Kras(G12D) mouse model." Diabetes. 2012 May;61(5):1250-62. doi: 10.2337/db11-1109. Epub 2012 Jan 20.

[45] Butler, et al., "Marked expansion of exocrine and endocrine pancreas with incretin therapy in humans with increased exocrine pancreas dysplasia and the potential for glucagon-producing neuroendocrine tumors.." Diabetes. 2013 Jul;62(7):2595-604. doi: 10.2337/db12-1686. Epub 2013 Mar 22.

cancer among users of Incretin-based therapies.[46]

The mechanism by which Incretin-based therapies cause pancreatic cancer is based on sound science. Incretin-based therapies target specific pancreatic cells, including duct cells, encouraging the proliferation of both, and, while that model *alone* would survive a preponderance of the evidence standard, existing research has taken the next steps and shown both the acceleration of PanIN lesions (both in animal models and in human pancreata) and a statistical elevation in pancreatic cancer among the users of Incretin-based therapies. Whether this is "cherry picking" or not is an issue as to the weight of the testimony, not the admissibility; the Court's role here is to serve as gate-keeper, not fact-finder, and the evidence suggesting a causal link was sufficient to prompt reviews by the FDA, and calls by the Institute for Safe Medication Practices[47] and the American Diabetes Association[48] for further investigation, including publication of patient-level data. These are not wild speculations by lawyers; they are the subject of intense investigation by the scientific and medical communities.[49]

Defendants, naturally, disagree, on the basis of their own studies and clinical data — clinical data which has not been provided to the Plaintiffs, data which Defendants apparently hope will never make it to the Plaintiffs or their experts, given their proposed *Daubert* scheduling. In support of

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[46] Elashoff, et al., "Pancreatitis, pancreatic, and thyroid cancer with glucagon-like peptide-1-based therapies." Gastroenterology. 2011 Jul;141(1):150-6. doi: 10.1053/j.gastro.2011.02.018. Epub 2011 Feb 18. Results confirmed by Nauck, et al., "Do GLP-1-based therapies increase cancer risk?" Diabetes Care. 2013 Aug;36 Suppl 2:S245-52. doi: 10.2337/dcS13-2004.

[47] <http://www.ismp.org/quarterwatch/pdfs/2012Q3.pdf>.

[48] <http://www.diabetes.org/newsroom/press-releases/2013/american-diabetes-association-incretin-therapy.html>.

[49] *See, e.g.*, Prof. Fred Gorelick, "GLP-1 based therapies and pancreatic disease: review of potential mechanisms," presented at the EASD Barcelona 2013 Conference, *available at* <http://www.easdvirtualmeeting.org/resources/6257>.

upending the case management schedule they agreed to and replacing it with an unprecedented, unworkable schedule in which general causation challenges begin before general causation discovery is concluded, Defendants cite little more than their own self-serving conclusions based on secret data, the AACE/ACE Consensus Statement, and a report from the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP).

The AACE/ACE Consensus Statement by the "Task Force for Diabetes and Cancer" is open to more than a little doubt. The chairs both received funding from Merck and Bristol-Myers Squibb (which now owns Amylin); one chair received funding and/or consulting fees from every Defendant here, plus a dozen other pharmaceutical companies. Of the ten other "Task Force" members, all but one received funding or consulting fees from a company that sold an Incretin-based therapy, and more than half received funding specifically from the Defendants here. As the Consensus Statement concludes, "The conference, editorial assistance, and the consensus statement were supported by the AACE. Part of the costs of the AACE conference were deferred by grants from Amylin Pharmaceuticals, LLC; Bristol-Myers Squibb Company; AstraZeneca; Eli Lilly and Company; Merck & Co, Inc; Novo Nordisk, Inc; and Sanofi-Aventis, US."[50]

[50] *See also* Angell, "Industry-Sponsored Clinical Research-A Broken System," JAMA Vol. 300, No. 9, Sept. 3, 2008 ("Two recent articles underscore the problem: one showed that many publications concerning Merck's rofecoxib that were attributed primarily or solely to academic investigators were actually written by Merck employees or medical publishing companies hired by Merck (Ross JS, Hill KP, Egilman DS, Krumholz HM. Guest authorship and ghostwriting in publications related to rofecoxib: a case study of industry documents from rofecoxib litigation. JAMA. 2008;299(15):1800-1812.); the other showed that the company manipulated the data analysis in 2 clinical trials to minimize the increased mortality associated with rofecoxib. (Psaty BM, Kronmal RA. Reporting mortality findings in trials of rofecoxib for Alzheimer disease or

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The EMA CHMP review does not fare much better; on information and belief, the review was conducted by consulting experts like Claes-Göran Östenson, who served on the "Global Portfolio Advisory Board (concerning insulin and incretin drugs)" for Novo Nordisk and is the Principal Investigator for Eli Lilly's "CHOICE" study regarding Byetta and for a study of a new SGLT-2 inhibitor being developed by Boehringer-Ingelheim, and Michael Feher, who consulted with Novo Nordisk over an new diabetes drug and with Merck over Januvia.

Yet, even with such a stacked deck, and even though the EMA CHMP was at the mercy of whatever data Defendants chose to give them, the EMA CHMP nonetheless noted that "studies performed in some other disease models by academic groups may give some plausibility with respect to a possible mechanism for an increased risk of pancreatitis and pancreatic cancer in patients treated with GLP-1 based therapies," and that "long term consequences of stimulation of beta-cells and suppression of alpha cells as well as possible effects on exocrine pancreas are largely unknown and therefore some uncertainties exist." The EMA CHMP even noted the problems with performing a statistical analysis to detect a causal link to pancreatic cancer: "Considering that pancreatic cancers are very rare, large populations would need to be studied for a substantial duration to detect a possible increased risk."

The EMA CHMP thus applauded the additional studies underway, and recommended continued monitoring.

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cognitive impairment: a case study based on documents from rofecoxib litigation. JAMA. 2008;299(15):1813-1817). Bias in the way industry sponsored research is conducted and reported is not unusual and by no means limited to Merck.(DeAngelis CD, Fontanarosa PB. Impugning the integrity of medical science: the adverse effects of industry influence. JAMA. 2008;299(15):1833-1835.).

CONCLUSION

Once viewed in context, the motivations behind Defendants' desperate rush towards *Daubert* are clear: the science is not getting better for them, it is getting *worse*, and they apparently fear that their own data, or the ongoing studies, or both, will move the general causation evidence from "reliable" to "indisputable." Defendants' demand that the agreed-upon scheduling agreement be dissolved in favor of an unprecedented, illogical, time-wasting *Daubert*-before-discovery schedule suggests more than a hint of desperation in their camp. Accordingly, Plaintiffs request this Court use a standard schedule — as agreed to previously by the parties and thereafter endorsed by the Court.

Dated: February 10, 2014 Respectfully submitted,

/s/ Ryan L. Thompson
Ryan L. Thompson
WATTS GUERRA LLP

/s/Maxwell S. Kennerly
Maxwell S. Kennerly
THE BEASLEY FIRM

/s/Hunter J. Shkolnik
Hunter J. Shkolnik
NAPOLI BERN RIPKA SHKOLNIK

/s/Tor A. Hoerman
Tor A. Hoerman
TORHOERMAN LAW LLC

Attorneys for Plaintiffs

CERTIFICATE OF SERVICE

The undersigned hereby certifies that a true and accurate copy of the foregoing was served upon all counsel of record via the Court's CM/ECF Filing System this 10th day of February 2014.

s/ Ryan L. Thompson
Ryan L. Thompson